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Session: Gender Differences in Infectious Diseases
Date: Saturday, April 5, 2014
Time: 10:15-12:15
Room: Room 1.60

Sex differences in immune responses to vaccines

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Sex differences in susceptibility to infections, and their clinical course and outcome, have been well described in the literature. Thus adult females generally mount more pronounced pro-inflammatory innate and adaptive immune responses to viral and bacterial infections than males, and generally males have poorer outcomes in bacterial septic shock. Despite this, few studies consider the effect of sex when analysing responses to vaccines. Females have been shown to mount stronger humoral responses to vaccines compared to males and have higher rates of adverse reactions. Additionally, adult females have been shown to up-regulate more innate immune response genes following yellow fever vaccination than males. The paucity of literature, particularly in regards to infant immunity, prompted us to examine the influence of sex on vaccine responses in more detail. We conducted a series of immunological vaccine studies in infants living in The Gambia, West Africa. We analysed for sex differences in the immunological profiles following administration of measles vaccine (MV) or diphtheria, tetanus, whole cells pertussis combined vaccine (DTwP) to nine month old infants. Assays included whole human transcriptional profile analysis, vaccine antibodies, *in vitro* cytokine release in response to innate stimuli or cognate antigens, as well as intracellular cytokine staining to enumerate polyfunctional T cells. There were clear sex differences in post-vaccine immunity for most of the parameters tested. Generally, male infants had more pro-inflammatory innate and adaptive immune response profiles compared to females of the same age. The sexes differed in their transcriptional profiles following vaccination, with distinct sets of genes being differentially expressed. By contrast, vaccine induced antibody responses to MV and DTwP were equivalent in male and female infants. The observation of sex differences in the immune responses elicited by vaccines has a number of important implications. It suggests that sex should be taken into account in vaccine studies; particularly for novel vaccines and in vaccine safety trials. Failing to do so may miss important data. The mechanisms are not yet known, but differences in sex hormone levels and expression of X-linked immune responses and microRNAs genes may be involved.

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Sex discrepancies in vector-borne infectious diseases

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Infectious diseases occur disproportionately in men and women. Furthermore, the severity and outcome of infections are often sex-related. What are the underlying factors for these discrepancies? Some studies have pinpointed a marked sex difference in immune response. Females typically develop stronger innate, cell-mediated and humoral immune responses with fluctuations according to hormonal levels that vary naturally during the menstrual cycle, pregnancy, menopause or with the use of hormones as contraceptives or hormone replacement therapy. Male sex hormones have been implicated in immunoregulation. Testosterone causes a decline in certain immune responses and young men are often at greater risk of severe infections compared to women or older men. The hormonal household and the skin chemistry also influence the attractiveness of men and women to mosquitoes and other vectors.

On the other side of the equation, gender factors play a role in susceptibility to vector-borne infections. Behavioural, occupational and cultural differences lead to gender differences in vector exposure, use of personal protection measures and health seeking practices.

This presentation highlights sex discrepancies in infections transmitted by mosquitoes and ticks and places this evidence in context in terms of physiological factors and gender-specific behaviour.

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Gender differences in tuberculosis

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Tuberculosis shows marked differences between males and females in terms of detection and notification, progression to disease after infection and disease outcome, as well as the social consequences of the disease. Both biological sex and socially constructed gender differences are important determinants of tuberculosis and they interact to produce differences in risks and vulnerability. Furthermore, these factors interact with other social determinants to effect health outcomes. The social structure of many societies in low-income countries today relies on women having a double or triple workload, including household,

agricultural and/or waged work. As women are also the primary carers in the family, the impact of tuberculosis is severe for individual families as for society in general.

Evidence of gender disparities from studies in collaboration between Karolinska Institutet and Hanoi Medical University as well as from the literature include that TB disease in some contexts could influence possibilities to marry, to stay married and even so via proxy, since in particular women in a family with TB disease would face barriers to marriage. Married women with TB may be at risk of divorce, of their husband taking a second wife, or of being sent to their natal homes. In Pakistan, marriage prospects as perceived by parents influence treatment taking among unmarried children.

Conclusions: Gender dynamics are thus key factors affecting the risk of a person becoming infected and developing tuberculosis as well as his or her access to health information, health-seeking behaviour and treatment outcome. In addition, gender norms and gender inequality influence coping capacities and the social consequences of having tuberculosis.

Future research needs include: Population-based studies in multiple settings together with sentinel surveillance activities are recommended to get unbiased data on TB incidence and prevalence. Semi-active case-identification in target populations, acknowledging the devastating effects of the interaction between gender and HIV, eg. TB screening linked to PMTCTMore basic science initiatives to investigate sex differences in immune response to infection and determinants of disease development and the link to sex specific hormone levels

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Sex differences in antiretroviral therapy efficacy and toxicity

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The development of effective combination antiretroviral therapy (ART) has transformed the management of HIV infection over the past twenty years, yet many challenges remain. Globally women comprise half of all people living with HIV, yet women have been underrepresented in most clinical trials evaluating the efficacy and safety of ART. More recently several groups of investigators have designed and analyzed clinical trials with a goal of evaluating sex difference in ART. These studies have suggested differential rates of toxicity in women and men and some important differences in response rates to standard treatments. This presentation will review recent findings on sex differences in the pharmacokinetics of protease inhibitors and non-nucleoside reverse transcriptase inhibitors and highlight sex differences and efficacy from recent clinical trials. Finally research priorities in the area of sex differences in HIV therapy will be suggested.

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Rickettsial diseases in Eastern Africa

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Rickettsial diseases have been described in Eastern Africa for over 50 years. These include: epidemic typhus (*Rickettsia prowazekii*), murine typhus, (*Rickettsia typhi*) and Mediterranean spotted fever also known as Kenyan tick typhus (*Rickettsia conorii* subsp. *conorii*). Contemporary reports describe these same diseases in addition to new rickettsiae and rickettsial diseases utilizing serological and molecular techniques. Some of the new agents and diseases include: *Rickettsia felis* (flea-borne spotted fever), *Rickettsia felis*-like organisms (e.g. *Candidatus* Rickettsia asemboensis), *Rickettsia africae* (African tick-bite fever), *Rickettsia africae* variants (e.g. *Rickettsia* sp. AVR4), *Rickettsia aeschlimanni* (an unnamed tick-borne rickettsiosis), *Rickettsia sibirica* subsp. *mongolitimonae* (lymphangitis-associated rickettsiosis), *Rickettsia conorii* subsp. *israelensis* (Israeli spotted fever) and *Candidatus* Rickettsia kulagini. These reports indicate that individuals residing in and those visiting Eastern Africa are at risk of various rickettsial diseases. Unfortunately, the dearth of comprehensive studies of the prevalence and distribution of these rickettsiae or the incidence of the particular rickettsioses hinder development of proper mitigation strategies.

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Rickettsioses in Africa: A paradigm of new or emerging infectious diseases

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Rickettsioses were considered 20 years ago as being rare diseases with one species of Rickettsia transmitted by ticks, per continent. Modern tools have been disrupting the perception of the world of rickettsioses. The first works were performed directly on biting arthropods (ticks, fleas, mites) that helped to identify a number of microorganisms putatively involved in human diseases. This difficulty to use classical tools for diagnosis in patients (such as culture), prevented for a long time the identification of human cases. The development of molecular tools based on skin (biopsies and swabs), and blood shows the huge frequency of rickettsioses. In rural Asia, rickettsioses (scrub typhus and murine typhus) are among the most frequent cause of unexplained prolonged fever. In western and eastern Africa, rickettsioses (mainly *R. felis*) are the